Aus dem Pathologischen Institut der Universität Basel
(Vorsteher: Prof. Dr. med. A. Werthemann)
Arbeit unter Leitung von Prof. Dr. med. S. Scheidegger

TUBEROSE SCLEROSIS

(Bourneville's disease)

INAUGURAL-DISSERTATION

zur Erlangung der Doktorwürde der Medizinischen Fakultät
der Universität Basel

vorgelegt von

GEORGE CHAKMAKIS

von Lowell (Massachusetts, USA)

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Tag der Promotion: 29. Mai 1967

PROBLEMS OF THE TUMOUR

A brief survey of tuberous sclerosis complex, a term coined by Moulton in 1942, shows that in preceeding years the original name was Bournevilles disease, so called after Bourneville in 1880. It is congenital, with tumour like malformations of ectodermal and mesodermal derivation and may manifest itself at any age. In 1908 Vogt defined the syndrome as adenoma sebaceum, epilepsy, and mental dificiency. Later, in 1911, Sherlock termed this complex epiloia. In this discussion, however, we will refer to this disease as tuberous sclerosis complex, due to the fact that it derives its name from the autopsy findings of the brain, peculiar to this disease. These consist of potatoe-like sclerotic patches, mainly composed of neuroglial proliferations and scattered over the cerebral cortex and rarely in the cerebellum. They are multiple and seldom solitary. There are two varieties as described by Pelizzi in 1901. The first, a «hardening blanching and widening of a gyrus, the crown of which is flattened and smooth» and the second a «rounded, flattened nodule, the surface of which is roughened and dimpled and which is sometimes slightly elevated above the level of the neighbouring gyri from which it is superficially demarcated by a surrounding sulcus». They are hard to the touch, sometimes having a consistancy as hard as cartillage, and rangeing from 0,5 to 2 cm in diameter. These changes in the cortex are irregularly distributed, some of the favoured sites being the sulcus terminalis, which has projections in the lateral ventricles, thalamus or nucleus caudatus. There may be an obstruction of cerebral spinal fluid, due to iron-calcium deposits in the foramen Monroe or foramen Sylvius of the ventricles.

Histo-patological examination of the sclerosed areas shows increase of astrocytic nuclei, scanty nerve cells, enlarged bizarre shaped cells and large oval plump cells with no processes. In the

sulcus terminalis projecting into the lateral ventricles like «gutterings of a candle» are multiple small, tumour like nodules, of fibro cellular character. The latter can contain numerous blood vessels with thickened walls, fibrillary astrocytes, iron calcium deposits, rings of collagen or reticulin, and abnormal nerve cells. Although these tubers are infrequent in the cerebellum, in our particular case they are present so mention of the microscopical findings in general, should be made. We have gleaned from the available literature, that heterotopic clusters of giant-cells in the white matter, monster cells in the layer of Purkinje's cells, widespread loss of Purkinje's cells and lobular atrophy, may occur.

HISTORY OF THE ILLNESS

The infant, H. S. a fairly strongly built male child, premature, normal birth, survived only two days. Directly after birth, 36 hours old, cyanosis, breathing difficulty, and circulatory collapse occurred. The child was removed from place of birth, to a children's hospital, where they found substernal retraction, slight cyanosis, and increased respiration of 80/min and heart frequence of 160/min. Tle liver was enlarged; 2 to 3 transverse fingers. The thorax plate showed a large heart, which almost filled the thoracic cavity.

Therapy. Oxygen, digitalis, Cidelanid, Terramycin depot. The condition of the child remained unchanged and at the age of 51 hours, the colouring changed to ash-grey, and the heart stopped.

FAMILIAL HISTORY

One of the more interesting factors in the familial story would appear to be a tendency for several of the births to have been premature, on the mothers side. The child's mother was, herself, premature, and had «blue spells» until the age of six months. However, the course of her childhood after this time, shows nothing of specific importance. The pre-natal period was unevent-

ful and birth normal, although premature. As Doctor's assistant she did assist in the taking of X-rays during the pregnancy, which may or may not have some bearing on the case. There are four other children in her family, all in good health, the brother also having been prematurely born. One sister had a premature, still-born child. The grandmother and grandfather are living and are in good health. The grandfather had ricketts as a child and heart valve failure. His eyesight is poor. The child's father, a textile worker, suffered from severe migraine headaches accompanied by vomiting during the ages of 8 to 14 years of age, but since this time is in good health. The grandmother and grandfather are living, the former having migraine headaches and the latter suffering from a liver complaint, which may be the result of excessive intake of alcohol. The great-grandmother on the father's side, is living, one of twins, both of whom have had hearing difficulties since birth.

PATHOLOGICAL-ANATOMICAL FINDINGS

Child: Hanspeter Scheurer. Born: Oct 5, 1962. Age 1 Day old.

Case 1580/62

Cadaver of a fairly strongly built male infant. Rigor mortis is not strongly developed. Many blue-red lived spots on the extremities, which do not disappear on pressure. Skin gray-red, fairly elastic. Yellowish undertone in the face, especially on eyelids, and on abdomen. Sparse hair on the head, externally no malformations or injuries to be seen. The finger-nails do not quite reach the finger tips. Right testicle lies in the inguinal canal. Left testicle in the scrotum. In distal femur epiphyse a small bone nucleus can be observed. The pupils are round, medium wide, identical. The sclera is a dirty grey yellow. The subcutaneous fatty tissue is meagrely developed, grey white. The abdomen is at the level of the thorax.

The peritonieum is shiny. The intestal loops are distended. The liver extends beyound the rib-cage in the MCL to LHF. The

spleen lies under the rib-cage. The external orifices of hernial sack are closed. The diaphram reaches the height of the 5 ICS.

The rib cartilage cuts easily. The lungs are sunken back when the thorax is opened.

The heart is double the size of the cadaver and fills the thoracic cavity completely.

The pericardial sac is fragile and shows a shiny inner surface. The heart shows a coarse brittle outer surface. The right ventricle especially, is sharply arched on the ventricle wall, as is the left ventricle apex. The heart will be removed in connection with the throat organs and the lungs. There is no liquid in the pleural cavity.

The heart shows a clearly widely dilated left ventricle with a rather thin ventricle wall. In the region of the left ventricle apex one can observe a good haselnut sized, somewhat undefined, unclear, grey yellow moist nodule. A similiar nodule, rather more clearly defined is to be found in the septem intraventriculare. It is fairly intensively yellow in colour. A somewhat smaller, barely haselnut sized, nodule can be seen in the septum, sitting broadly based in the right ventricle. The right ventricle is clearly dilated, thin walled, both atrium medium wide, the tricuspid and mitral valves are fragile and shine in water rays. Pulmonal and aorta valves are lying according to rule, although fragile. The coronary vessels go correctly out of the aorta. The ventricle septum is intact. The atrium septum is likewise intact, the foramen ovale can be probed throughout. Also the ductus botalle is penetratable. No malformations on heart to be seen. The large vena cava superior and interior flow correctly into the right atrium, the pulmonary veins into the left atrium.

The lungs show a shiny pleura. All the lobes are plethoric and full of fluid, and have, particularly in the marginal zones, expanded, air free, slack, regions. Infiltrated areas are not to be observed.

The bronchi show delicate mucosa and contain some mucus. The pulmonary vessels are soft.

The tongue shows an undeveloped follicle apparatus on the base. The tonsils are small, clefted. The esophagus is soft walled, also the trachea. Bifurcations paratracheal as well as the hilus

lymph nodes are grey red, soft, moist and small. The aorta is medium wide in the aortic arch, soft walled. Neck and arm vessels go according to rule. The thyroid glands show on cutting, 2 medium sized, grey brown, slightly colloid, shiny lobes.

The spleen is medium sized, its outer surface smooth, and on cutting, the tissue is fairly plethoric.

The liver is somewhat larger than medium size, and shows a smooth outer surface, and a soft capsel. On cutting, the tissue is fairly soft, plethoric, somewhat ruptured, in parts clearly spotted, the lobe structure is difficult to observe. The coarse bile ducts are penetratable on pressure. The gall bladder has a thick wall and contains a quantity of sticky, dark green gall.

Both adrenal glands are in the correct position. The left is very mutilated, due to the left kidney being removed post-mortem, for virology tests. The right adrenal gland is medium sized, with a narrow deep yellow cortex, which is not clearly defined from the grey medula.

The right kidney has a well preserved rencule sulcus, the fibrous capsel is soft, easily reomved. The tissue is plethoric on cutting, in the pyramids there are grey yellow striped stratifications.

The pelvis renalis is medium wide, the ureter narrow. The kidney on the left side is missing, as before mentioned, having been removed post-mortem.

The urinary bladder is examined. The rectum contains some sticky green meconium and has a delicate mucous membrane. Both testicles are small, lie correctly, as does the ductus epididymus.

The processess veriformes is fairly long, narrow, the coecum and the remaining large intestines contain rich, sticky green meconium. They have a delicate mucosa without ulceration.

The small intestines are medium wide, soft. The stomach contains some yellowish, slimy fluid and a mucosa with a clear relief, no ulcerations or scars to be seen. The pancreas is fairly firm on cutting, showing a clear lobe structure. The abdominal aorta is soft-walled, the spinal column physiologically curved.

The skull will be opened by the Tentorium method. Falx cerebri and tentorium cerebelli are intact. The soft leptomeninx are moist and plethoric. The basal brain vessels are narrow.

The brain in general has little blood hroughout, and appears soft. The cortex and medulla are only indistinctly distinguishable. The subcortical grey nuclei are medium sized and symmetrical. The brain tissue is soft in this area too. The cerebellum somewhat highly vascularised. Pons and extended medulla is firmer in general than the cerebral medulla. Inspection of the ventricle ependyma, especially in the region of the lateral ventricles, shows a few more yellowish, partly light grey coloured areas, which demarcate themselves indistinctly. These herds are distinguishable more easily by palpation than with the naked eye. Several such regions of solidification and hardening can be observed on palpation of the brain slices. They are partly to be found in the cerebral cortex, in the region of the medulla and again in the area of the ventricles. These herds measure in general, between 10 and 5 mm. They are often long, and frequently arranged subcortically and travel in the direction of the cortex. These herds are fairly numerous when the brain is dissected into thin slices and carefully palpated, but sometimes they can only be detected by palpation. They are considerably more numerous than might be presumed with the naked eye. In the cortex cerebellum, which is rather undeveloped, one can find no true herds of this type, whereas in the medulla of the cerebellum, in the neighbourhood of the nucleus, they are present.

MICROSCOPIC EXAMINATION

Myocard:

(Apex of left ventricle) medium wide muscle fibres with diffuse finely beaded fatty degeneration. Large distended, vasicular raised cells stored between the muscle fibres. They are irregularly arranged, bordered hazily against the surrounding myocard. These cells contain, here and there, fine beads of fatty material. When stained for glycogen, with Best carmin and P.A.S. the cells are found to be very rich in glycogen. The nuclei of the cells vary somewhat in size. Mitosis and atypical nucleus are not observed. A direct conversion of muscle fibres in the described vacuolised large cells is not evident. The vacuolised cells are nevertheless very blurred against the musculature.

Tumour nodes in the right ventricle: show the same construction as the before described. Large cells with rather small nuclei and optically empty cytoplasma. These cells also contain abundant glycogen.

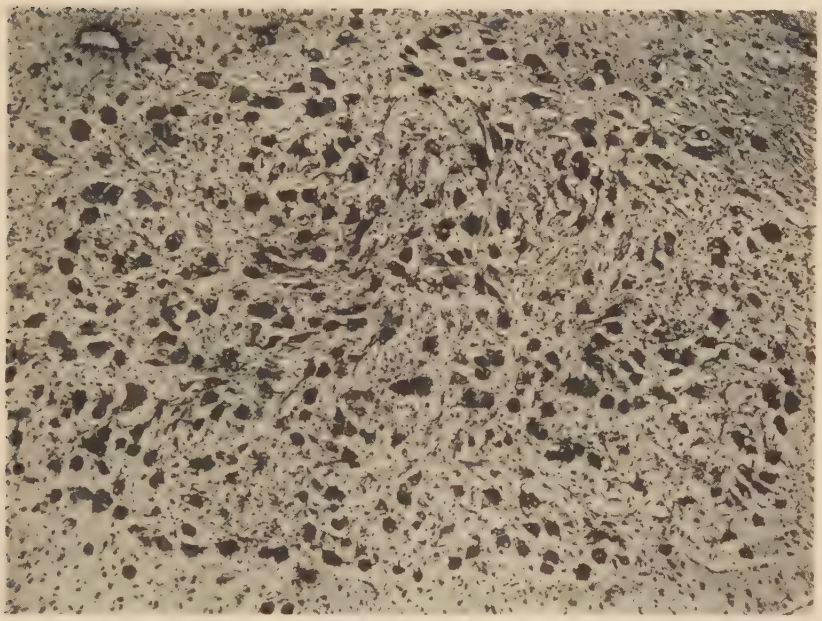

Abb. 1
Sclerotic patch or «tuber» in the brain with gliacell proliferation.
SN 1580/62 Vergrößerung 1:100

Lungs: show fairly massive blood aspiration. There is fresh blood in the alveolen and in the small bronchioli. Atelectase herds can be seen close by. No hyalin membranes.

Liver: shows diffuse, fine to medium sized beads of fatty degeneration. Portal area somewath wide, lobe structure preserved. Fairly numerous foetal blood building herds.

Kidneys: adequately developed for the age. The distal tubules show fine beaded fatty degeneration. There is a fairly strong blood congestion.

Epikrise: It is a case of a typical rhabdomyoma of the heart muscles.

MICROSCOPIC EXAMINATION

Brain:

The brain when examined microscopically, over a general survey of cuts with Nissl preparation, shows nodes in several places. These nodes are distinctively rich in cells. They are found in many places on the convexity, especially in the subcortical area, extending into the medulla and go, partly, over the actual cortex.

Special large cell constructions are found in these nodes, which are in part a type of ganglion cell, and also in part a type of mutated glia cell. There is a glia proliferation in general around these nodes. Multitudinous astrocyte and microglia cells are also found here. In several places, not only in areas with such herds of node proliferation, the cerebrum cortex proves to be somewhat lacking in cells. The architecture of the individual cortical layers is preserved, but there is a lack of glia cells. In the region of such nodes there are the so called monster glia cells, which appear partly through a prominent fibrillary construction. Here and there cells show fine inclusions, others are poor in extensions and resemble large balloon shaped elements. There are no plasmatic inclusions in these cells and the nucleus is often displaced. There are also node constructions in the region of the ventricles. The ventricle ependyma is somewhat loosened. Sometimes the nodes have developed under the ependyma and have caused a bulging of the ependyma coating.

The nodes in the region of the ventricles are extremly rich in cells, but these do not have the same large elements as the nodes in the area of the cortex. Spindle cells sometimes appear here and these often have a fibrous structure. True calcification is not present. There are especially rich astrocytes in the ventricle nodes.

An atrophy of the cortex is evident in general in the cerebellum and there is a marked lack of cells here. Purkinje cells are absent in large stretches and are also partly shrivelled. The lobules of the cerebellum are generally poor in cells, the granular layer particularly undeveloped. Between the gaping cerebellum lobules, the leptomeninx is often decidedly constructed and fills the gaps. The leptomeninx is plethoric in general. The ependyma of the 3rd and 4th ventricles is intact. The olives are well formed.

PATHOLOGICAL-ANATOMICAL DIAGNOSTIC MANIFESTATIONS

Tuberous sclerosis and rhabdomyosarcoma of the heart muscles

Multiple small nodules of the cortex (tuber) with monster glia cell developement.

Rhabdomyoma of the right ventricle, broadly based on the septum interventriculare. Haselnut sized intramyocardiale rhabdomyo of the septum interventriculare and the left apex of the left ventricle. Slackening and dilation of both, especially of the right ventricle. Open foramen ovale, open ductus botalli, oligaemie of the myocard.

Extensive atelectasis of buth lungs. Congestion of liver. parenchyma. Passive hyperaemia of the leptomeninx.

DISCUSSION

Tuberous sclerosis is a congenital disease, as has been previously stated. However, it can be observed from the available literature, that the ages of its manifestation and rate of progress vary considerably. Our case, for example, was apparent at birth. There have been similar cases recorded commencing at birth, while others have shown the onset of the disease at various ages up to and including 49 years of age.

W. Fischer stated that rhabdomyomata, if occurring at all, is seen only in children. R. Debre, S. Thieffry, Mozziconacci, Bargeton and Ramade, diagnosed rhabdomyomata in 58 % of 41 observations, all of whom were children under the age of 3 years, with tuberous sclerosis. Our case also showed rhabdomyomata. G. Weber described a case of a five month old girl with tuberous sclerosis and cardiac rhabdomyomata. He suggests, for the pathologic complex of tuberous sclerosis, the term «hamartoblastic myoglycogenic neurotuberous dysplasia» which seems to suit the anatomico-histopathological description of many patients afflicted with tuberous sclerosis complex.

The mode of inheritance possibilities should also be clarified in our case and in others. Marshall, Saul and Sachs Jr. in their analysis stated «the disease is due basically to the presence of rare autosomal dominant gene. The trait is known to skip a generation and reappear: it also arises occasionally in persons whose ancestors are not known to have been affected». B. H. Kerman observed two cases of children with no evidence of a hereditary factor. P. W. Miles and J. M. Dixon described a case of three siblings with no family history and L. Marchand, M. Brissot and Boittelle-Lentulo two cases which occurred in healthy families. Borberg examined a total of 37 cases of tuberous sclerosis, belonging to 35 families, of which 21 of the families were without inheritance. As will be seen these are all comparable to the case under discussion, which was also without inheritance, although there appears to me to be certain suspicious factors in the family history of our particular case. It is to be noted for example that. M. Le Franc describes 4 cases of tuberous sclerosis in which the fathers of the children afflicted in 3 cases, were inveterate alco-

holics. Fontan, Verger, Marchand and Couteau also examined a family with 3 girls and 2 boys, the mother and the 3 daughters showed the picture of tuberous sclerosis and the father was an alcoholic. Although it cannot be said that our case is exactly parallel to these, in this respect, it can be stated that the grandfather of the child is a heavy drinker and both the mother and father of the child volunteered the information that a certain amount of alcohol was consumed at the time the child was conceived. I put this comparison forward as a possible factor to be considered. Due to the fact that tuberous sclerosis is a rare disease it is difficult to pursue the possibilities further, literature on the subject not being very abundant and the incidence of cases scarce.

It appears that there is no prophylactic course to be taken to prevent the appearance of tuberous complex- the data indicates that the congenital malformation occurs in a latent form already in the ovum, therefore, as has been suggested by D. Rodololfo, every effort should be made to prevent the maturing of such ova. Recognition of the complex and its symptoms is important and in cases of familial inheritance it would seem appropriate to induce abortion or recommend sterilization, an idea put forward by the Danes. Subjects with marked feeble-mindedness should be cared for in institutions. There have also been several successful results obtained radiologically and neurosurgically. Kirman suggests deep irradiation of the brain to reduce the epileptic fits. Dandy successfully removed the tumour by operation and F. K. Kessel suggest that a Torkildsen operation might be performed on inoperable cases. Dr. Harvey Cushing also removed a tumour in 1931 and the patient was still living 28 years later, which points to the fact that sugical intervention might be indicated in certain incidences.

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